

ATENT COOPERATION TREATY

(09-125329) 5060  
PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing:

17 December 1998 (17.12.98)

International application No.:

PCT/EP98/03427

Applicant's or agent's file reference:

4-30028/A

International filing date:

08 June 1998 (08.06.98)

Priority date:

10 June 1997 (10.06.97)

Applicant:

PORTMANN, Robert et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

13 November 1998 (13.11.98)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/03427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 199262	A	29-10-1986	
		AU 599024 B	12-07-1990
		AU 5631986 A	23-10-1986
		CA 1272201 A	31-07-1990
		CY 1751 A	03-06-1994
		DD 245874 A	20-05-1987
		DK 175686 A	19-10-1986
		FI 861573 A, B,	19-10-1986
		HK 1494 A	14-01-1994
		IE 58472 B	22-09-1993
		JP 1848050 C	07-06-1994
		JP 61243068 A	29-10-1986
		MX 9203628 A	01-09-1992
		PT 82400 B	17-08-1988
		SG 142293 G	31-03-1994
		US 4789680 A	06-12-1988

PCT

09/125.329  
WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 249/04, A61K 31/41</b>	<b>A1</b>	(11) International Publication Number: <b>WO 98/56772</b> (43) International Publication Date: 17 December 1998 (17.12.98)
---	-----------	---

(21) International Application Number: PCT/EP98/03427

(22) International Filing Date: 8 June 1998 (08.06.98)

(30) Priority Data:  
1404/97 10 June 1997 (10.06.97) CH

(71) Applicant (for all designated States except AT US): NOVAR-TIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).

(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VER-WALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1235 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PORTMANN, Robert [CH/CH]; Unterer Rütshetenweg 38, CH-4133 Pratteln (CH). HOFMEIER, Urs, Christoph [CH/CH]; Hauptstrasse 30, CH-4421 Pantaleon (CH). BURKHARD, Andreas [CH/CH]; Blotzheimerstrasse 29, CH-4055 Basel (CH). SCHERRER, Walter [CH/CH]; Habsburgerstrasse 62, CH-4310 Rheinfelden (CH). SZELAGIEWICZ, Mar-tin [CH/CH]; Christoph-Merian-Strasse 1, CH-4142 Münchenstein (CH).

(74) Agent: BECKER, Konrad; Novartis AG, Patent- und Marken-abteilung, Lichtstrasse 35, CH-4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**

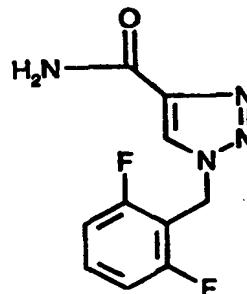
*With international search report.*

*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

(57) Abstract

The invention relates to the novel modification A or A' of the compound 1-(2,6-difluoroben-zyl)-1H-1,2,3-triazole-4-carboxamide of formula (I), its use for the treatment of epilepsy, and pharmaceutical preparations comprising this crystal modification.



(I)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>4-30028/A</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/EP 98/ 03427</b>	International filing date (day/month/year) <b>08/06/1998</b>	(Earliest) Priority Date (day/month/year) <b>10/06/1997</b>
Applicant  <b>NOVARTIS AG et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant

☒ the text has been established by this Authority to read as follows:

**CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTI-EPILEPTIC**

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/ 03427

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 11  
is directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/03427

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

- last line, between "its use" and "and pharmaceutical" insert  
"for the treatment of epilepsy,".

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03427

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D249/04 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 199 262 A (CIBA-GEIGY AG) 29 October 1986 cited in the application see the whole document, particularly example 4 ---	1-15
A	MÜNDEL K: "Der Einfluss der Formgebung auf die Wirkung eines Arzneimittels" Fortschritte der Arzneimittelforschung - Progress in Drug Research - Progrès des Recherches Pharmaceutiques, vol. 10, 1966, pages 227-30, XP002078506 Basel, CH --- -/--	1-15

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

23 September 1998

Date of mailing of the international search report

07/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Allard, M

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03427

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MÜNZEL K: "Galenische Formgebung und Arzneimittelwirkung / Neue Erkenntnisse und Feststellungen"</p> <p>PROGRESS IN DRUG RESEARCH - FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG - PROGRÈS DES RECHERCHES PHARMACEUTIQUES,</p> <p>vol. 14, 1970, pages 309-21, XP002078507</p> <p>Basel, CH</p> <p>-----</p>	1-15



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/03427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 199262 A	29-10-1986	AU 599024 B	12-07-1990
		AU 5631986 A	23-10-1986
		CA 1272201 A	31-07-1990
		CY 1751 A	03-06-1994
		DD 245874 A	20-05-1987
		DK 175686 A	19-10-1986
		FI 861573 A,B,	19-10-1986
		HK 1494 A	14-01-1994
		IE 58472 B	22-09-1993
		JP 1848050 C	07-06-1994
		JP 61243068 A	29-10-1986
		MX 9203628 A	01-09-1992
		PT 82400 B	17-08-1988
		SG 142293 G	31-03-1994
		US 4789680 A	06-12-1988

PATENT COOPERATION TREATY

PCT

REC'D 20 AUG 1999

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

MAR 20 2000

TECHNICAL CENTER 1600/2900

(PCT Article 36 and Rule 70)

09125329

Applicant's or agent's file reference 4-30028/A		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) <b>FOR FURTHER ACTION</b>	
International application No. PCT/EP98/03427	International filing date (day/month/year) 08/06/1998	Priority date (day/month/year) 10/06/1997	
International Patent Classification (IPC) or national classification and IPC C07D249/04			
Applicant NOVARTIS AG et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  13/11/1998	Date of completion of this report  18.08.99
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  Bu no Torres, M  Telephone No. (+49-89) 2399



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/03427

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-15 as originally filed

### Claims, No.:

1-15 as originally filed

### Drawings, sheets:

1,2 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 7, 11, 13-15.

because:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP98/03427

- ☒ the said international application, or the said claims Nos. 11 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 7, 13-15 are so unclear that no meaningful opinion could be formed (*specify*):

**see separate sheet**

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 1-6
	No:	Claims 8-10, 12
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-6, 8-10, 12
Industrial applicability (IA)	Yes:	Claims 1-6, 8-10, 12
	No:	Claims

**2. Citations and explanations**

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP98/03427

---

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/03427

- III. i) The subject-matter of claim 11 is directed to a therapeutic method of treatment (Art. 34 (4)(a)(I) and Rule 67.1 (iv) PCT).
- ii) The crystal modification A' cannot be "identical" to the crystal form A. Claim 7 does not include the lines of interplanar spaces or other characterizing features of the form A' which result as a consequence of the mentioned "defects in the crystal lattice". Therefore, the subject-matter of claim 7 does not fulfil the requirements of Art. 6 PCT, since it does not clearly and unambiguously define the crystal modification for which protection is sought.
- iii) Claims 13 and 14 have been defined as independent claims. The Applicant has not clarified to which form A or A' refer the characterizing bands in the FT-IR spectrum given in claims 13 and 14. Moreover, a better dependency among the claims should have been ensured. Therefore, no opinion can be given for the subject-matter of claims 13 and 14 (Art. 6 PCT).
- V. i) The following documents have been taken into consideration:
- D1 = EP-A-0 199 262  
D2 = Münzel K: "Der Einfluss der Formgebung auf die Wirkung eines Arzneimittels" Fortschritte der Arzneimittelforschung-Progress in Drug Research-Progrès des Recherches Pharmaceutiques, vol. 10, 1966, pages 227-30, XP002078506 Basel, CH  
D3 = Münzel K: "Galenische Formgebung und Arzneimittelwirkung" Fortschritte der Arzneimittelforschung-Progress in Drug Research-Progrès des Recherches Pharmaceutiques, vol. 14, 1970, pages 309-321, XP002078507 Basel, CH
- ii) Claim 1 of the present application relates to a crystal modification of the known compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, namely form A.
- A crystal form of the known compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide obtained by recrystallisation from ethanol has been already disclosed in D1 (see example 4). However, D1 does not disclose the lines with interplanar spacings (d values) of the X-ray powder pattern of said form or

other characterizing parameters thereof.

Crystal form A according to claim 1 is obtained by crystallization from methanol (see example 1) or water (see example 2). The differences of these processes for obtaining crystal form A when compared with the crystallization process disclosed in D1 appear to suggest the novelty of said form (Art. 33(2)PCT).

However, crystal form A' according to claim 8 is obtained by crystallization from ethanol (see example 5). Therefore, in the case of the crystal form A' the same crystallisation solvent as in D1 is used. Therefore, the subject-matter of claim 8 does not appear to be novel vis-à-vis D1.

D2 and D3 generally disclose the concept of polymorphism and its influence in the activity of pharmacological compounds. However, the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide has not been disclosed in D2 or D3. The subject-matter of claims 1 and 8 can therefore be considered to be novel vis-à-vis D2 and D3 (Art. 33(2) PCT).

- iii) The closest prior art is considered to be D1 which discloses a crystal form of the known compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide obtained by recrystallisation from ethanol. The mere existence of further polymorph forms of said compound is not in itself regarded as unexpected (see for instance D2, page 228). The problem underlying the invention is therefore considered to be the provision of further polymorph forms of the known compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with unexpected properties when compared with the known form disclosed in D1.

In this connection it has to be stressed that the alleged advantages of the crystal forms A and A' over the forms B and C cannot be taken as a support for the inventive step of said forms, since the disclosure of forms B and C is not comprised within the state of the art.

In the absence of any evidence for these unexpected properties, an inventive step cannot at present be acknowledged for the subject-matter of claims 1 and 8 (Art.33(3)PCT).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/EP98/03427

- VII. To meet the requirements of Rule 5.1(a)(ii)PCT, the documents D2-D3 should have been identified in the description and the relevant background art disclosed therein should have been briefly discussed.
- VIII. i) The crystal modification A' cannot be "identical" to the crystal form A. Claim 7 does not include the lines of interplanar spaces or other characterizing features of the form A' which result as a consequence of the mentioned "defects in the crystal lattice". Therefore, the subject-matter of claim 7 does not fulfil the requirements of Art. 6 PCT, since it does not clearly and unambiguously define the crystal modification for which protection is sought.
- ii) The compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide has at least four polymorph forms namely A, A', B and C and/or the one disclosed in D1. The Applicant has not confirmed as to whether the lines with interplanar spacings (d values) of the X-ray powder pattern as defined respectively in claims 1 and 8 are sufficient in order to clearly characterized the crystal forms A and A' (Art. 6 PCT).
- iii) The expression "a modification" used in the definition of claims 1-15 does not clearly and unambiguously define the subject-matter for which protection is sought. The expression "a modification" refers not only to **crystal** modifications of the known compound 1-(2,6-difluorobenzyl)- 1H-1,2,3-triazole-4-carboxamide but also to other vague and undefined possibilities of modification of said compound including "modifications" of its chemical structure. Therefore, the expression "modification" should have been replaced by "crystal modification " in the definition of claims 1-15 (Art. 6 PCT).
- iv) The expression "in essentially pure form" used in claim 9 does not clearly and unambiguously define the subject-matter for which protection is sought. Said expression should therefore have been replaced by "purity of >95%" as defined on page 10 of the description (Art. 6 PCT).